Off-label vaccines

An introductory guide for healthcare professionals

Before they can be placed on the market, all medicines, including vaccines, have to have a licence (marketing authorisation) for use in humans. Sometimes, however, it is necessary to offer a vaccine that is 'off-label'. This means that, although the vaccine is authorised for use, it's being used in a way that is slightly different from the strict terms laid down in its licence.

This leaflet describes the circumstances that can lead to vaccines being used 'off-label' and the reasons why this may be recommended.

How does a vaccine get a licence?

All vaccines have to be authorised by the UK Medicines and Healthcare products Regulatory Agency (MHRA), or the equivalent agency for Europe – the European Medicines Agency (EMA), before they can be placed on the UK market and advertised or promoted for use by the manufacturer. Vaccines are only submitted for licensing to the EMA or MHRA after they have been tried out on the target audience included in the licence, which could be children or adults, and fully tested to ensure that they are:

- acceptably safe
- able to provide protection against the disease they are designed to protect against, and
- manufactured to a high standard of quality.

This extensive testing process – from the first batch of a vaccine being made in a laboratory to its use in the general population – can take more than ten years. The detailed information on the results of testing in the laboratory and from clinical trials is then submitted for independent evaluation by the experts at the MHRA or EMA.

Only when these agencies are entirely happy with this information will the company be granted a licence to place the product on the market and to advertise or promote its use. Amongst other things, the licence specifies who can receive the vaccine, how many doses are required, what side effects may occur and how the vaccine should be handled and stored.

What does it mean for a vaccine to have a licence?

It means that the vaccine has been approved for use in certain people to protect against certain diseases and that the manufacturer can advertise or promote the use of the product for this purpose. The licence reflects only the specific situations in which the vaccine was studied before the company submitted data to the licensing agency. So, for instance, a licence may specify use in babies, but not older children, or it may specify use in adults but not in children. Or it may stipulate a schedule with doses given two months apart, but not at one or three months. This does not necessarily mean there is any suggestion that use in different situations is unsafe or ineffective, it just reflects the fact that trials need to have very strict criteria to ensure that the results are valid. It is often not feasible to study vaccines in every single population group or at every possible schedule before the vaccine is given its license. It would not be ethical to delay granting a licence whilst every possible scenario was studied because many people would then be denied the benefits of preventing an infection now.

Can a vaccine be used in a different way from that allowed in the licence?

A medicine or vaccine can only be marketed and promoted for use by the licence holder in accordance with the specifications of the licence. However, it is common in clinical practice for health professionals to prescribe a medicine for use in a different way from that stated in its licence. This is because the health professional has additional information on the medicine or has exercised his or her professional judgement and decided that the medicine would still be appropriate for this individual patient. This is often referred to as 'off-label' use. The legislation does allow for such situations and states that 'prescribers can use unlicensed and off-label medicines where there is no suitable alternative.' The responsibility for such use rests with the health professional.

'Off-label' use of medicines is fairly common, particularly in children, as most medicines are tested first in adults and conducting studies in large numbers of children can be difficult. Many vaccines are designed to be used in children and have been tested in this age group, and so 'off label' use of vaccines is much less common, but does occur from time to time. This is usually based on the recommendation of the Joint Committee on Immunisation and Vaccination (JCVI) – a UK committee made up of many independent experts on all aspects of vaccination.

Why are patients offered 'off-label' vaccines?

All routine vaccines currently used in the UK are licensed to be placed on the market. So, as well as having the data to support their safety and efficacy in accordance with the licence, it means they have been manufactured to a high standard and have undergone independent batch release. Sometimes, however, clinical experts on JCVI recommend that the vaccine should be used in people who were not included in the initial trials or recommend that the number or timing of the doses is different from

that used in the trials. As these situations were not specified in the licence this would mean the vaccine was being used 'off-label'. This recommendation is normally based on additional evidence presented to the committee that may have been obtained by a research group independent from the manufacturer. Sometimes it reflects the expert clinical judgement of the members based on their understanding of how vaccines work in different patient groups.

When a vaccine is being used 'off-label', it means that experts have advised that there are clear benefits of using the vaccine in this way and that the vaccine is still considered to be safe and effective. So 'off-label' use of vaccines does not mean they are unlicensed – they are licensed for use in different people or to be used in a slightly different way from the UK recommendation.

Often, the information gained from off-label use is then used by the manufacturer to apply to modify the licence to include these different uses.

Who decides when 'off-label' vaccines should be used?

Sometimes, after the EMA or MHRA has licensed a vaccine, circumstances change – such as an outbreak of a disease which necessitates the vaccine being used in a different population. Sometimes, new data emerges, which the manufacturer may not have produced themselves, and so it is not yet reflected in the licence. For example, an independent study may show that the vaccine works just as well at a different schedule (e.g. two doses six months apart instead of three doses at monthly intervals). Such studies are often conducted independently to ensure that the vaccine fits into the existing UK schedule, avoiding additional visits or unnecessary injections. In these situations, a recommendation may need to be made that is different from the terms of the licence, so that as many people as possible can benefit from the protection offered by the vaccine.

For the national vaccine programme, these decisions are usually taken by the JCVI. Most commonly, they involve recommending that a vaccine that is licensed for one group of patients can be used 'off-label' in another age group, or that a vaccine may be used at a different schedule from that in the licence.

Are there any examples of vaccines being used 'off-label' successfully in the past?

Some years ago, a vaccine against pneumococcal disease (PCV) was introduced into the routine childhood schedule in the UK to protect babies against serious diseases like meningitis and blood poisoning. The vaccine was licensed and recommended for three doses in babies, followed by a booster dose at around one year of age. Independent studies in the UK showed that the protection offered by three doses at two, four and twelve months, was just as good at offering protection to the target population. So the planned dose at three months was dropped, even though the licence stated that four doses should be given. The licence has now been amended to include the option of offering only three doses.

Another recent example is the use of a whooping cough vaccine in pregnant women. Over the past few years, the UK has experienced an increase in the number of whooping cough cases – many in babies too young to be vaccinated themselves. An urgent decision on how best to prevent deaths and serious illness in these babies was required. In 2012, JCVI agreed that the best way to protect these very young babies was by vaccinating women with pertussis (whooping cough) vaccine in weeks 28 to 32 of their pregnancy. This would ensure that babies were born with

high levels of antibody from their mothers. There were two vaccines suitable for boosting whooping cough protection in adults but neither had been tested on pregnant women, because such women are excluded from most clinical trials. However, data on the extensive use of vaccines with similar components was available and suggested that the vaccine would be safe and effective. One of the vaccines was therefore offered 'off-label' to pregnant women and, since then, around 60% of mothers have received the vaccine. The vaccine quickly resulted in a significant fall in the number of whooping cough cases and deaths in babies, and detailed analysis has shown that the vaccine was safe for the mother and the pregnancy. Based on the success of this vaccination campaign, and particularly the important data on safety and effectiveness in pregnant women generated in the UK, regulators should now be able to determine if use in pregnancy will be 'within label' in the future.

A further example is the HPV vaccine that is given to 12- to 13-year-old girls at school to protect them against cervical cancer. Based on studies in young adult women, the vaccine was originally given in three doses within a six-month period. New studies, however, have suggested that, in young girls, only two doses, given six months apart, are as effective as the three-dose courses in young adults. Based on the knowledge that young girls respond very well to vaccines and to make the programme work better with the school terms, JCVI has therefore recommended that the second dose of the HPV vaccine can be given between six and 24 months after the first, even though giving the second dose more than six months after the first dose is considered to be 'off-label'.

It can be seen, therefore, that 'off-label' can have several meanings.

In these examples, and in all other cases, the decision to use vaccines 'off-label' has been taken in the best interests of the patient and the wider public.

What if someone doesn't want an 'off-label' vaccine for themselves or their child?

Doctors are obliged to tell everyone, including parents on behalf of their child, that they are being offered an 'off-label' vaccine. In some instances, the vaccine is only offered in that way by the NHS. If they prefer not to have the vaccine themselves or for their child, as always, that is entirely their decision. However, it will only be for a very good reason that JCVI and/or the doctor has recommended that an 'off-label' vaccine is offered – so they will need to bear this in mind when making their decision. Not receiving a recommended vaccine could put themselves or their child at risk of contracting a serious infection.

More information

The General Medical Council has comprehensive information on this topic at: www.gmc-uk.org/guidance/ethical_guidance/14327.asp

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